REMARKS

Amendments to the Claims

Claims 1-10 were pending.

Claim 7 has been canceled without prejudice.

Claims 1-6 and 8-10 have been amended. Specifically, Claim 1 has been amended to recite: "An antitumor formulation, comprising an antitumor agent and hydroxyapatite particles having a maximum size of 5 μm, said antitumor formulation having reduced toxicity while maintaining the antitumor effects as compared to the toxicity of the antitumor agent administered without said hydroxyapatite particles, wherein said antitumor agent is blended with said hydroxyapatite particles and said hydroxyapatite is provided in an amount sufficient to reduce the toxicity while maintaining the antitumor effects." Support for this amendment can be found in the Specification, for example, at page 3, lines 15-18; page 3, line 34 through page 4, line 1; page 4, line 31 through page 5, line 24; page 6, line 4 through page 10, line 26; Tables 1-12 and original Claim 7.

Claims 1-6 and 8-10 have been further amended to recite "antitumor formulation" and "antitumor agent," instead of "antitumor agent" and "antitumor component," respectively, to better clarify the invention.

Claim 4 has been further amended to recite the full name designated for "UFT."

Claims 5, 6 and 8 have been further amended to recite "wherein said hydroxyapatite particles have a maximum particle size of..." to better clarify the invention.

Claim 10 has been further amended to recite "wherein said antitumor agent blended with said hydroxyapatite particles is pulverized." Support for this amendment is found in the Specification, for example, at page 5, lines 5-10.

New Claims 11-20 have been added.

Specifically, Claims 11-19 recite "A method of reducing toxicity of an antitumor agent without reducing the antitumor effects, comprising..." Support for the claim can be found in the Specification, for example, at page 3, lines 11-18; page 4, line 31 through page 5, line 24; page 6, line 4 through page 10, line 26; and Tables 1-12.

Claim 11 finds support from the Specification, for example, at page 3, lines 11-18; page 4, line 31 through page 5, line 24; page 6, line 4 through page 10, line 26; and Tables 1-12.

Claim 12 finds support from the Specification, for example, at page 4, lines 31-32.

Claim 13 finds support from the Specification, for example, at page 5, lines 5-7; and page 7, lines 26-28.

Claim 14 finds support from the Specification, for example, at page 5, lines 5-7; page 7, lines 4-10; and page 10, lines 12-18.

Support for Claim 15 can be found in the Specification, for example, at page 13, lines 9-21; and original Claim 2.

Support for Claim 16 can be found in the Specification, for example, at page 13, lines 9-16.

Claim 17 finds support from, for example, original Claim 3.

Claim 18 find support from the Specification, for example, at pages 31-34 (Tables 4); and from original Claim 4.

Claim 19 finds support from the Specification, for example, at page 5, lines 5-10 and page 34, line 15 through page 35, line 5.

New Claim 20 recites "An orally administered antitumor formulation, comprising an antitumor agent and hydroxyapatite particles having a maximum size of 5 μm, said antitumor formulation having reduced toxicity while maintaining the antitumor effects as compared to the toxicity of the antitumor agent administered orally without said hydroxyapatite particles..." Support for Claim 20 can be found in the Specification, for example, at page 3, lines 15-18, page 13, lines 9-16; and page 34, line 15 through page 35, line 5.

No new matter has been added. Entry of these amendments is respectfully requested.

Rejection of Claims 1-3, 9 and 10 Under 35 U.S.C. § 102(b)

Claims 1-3, 9 and 10 have been rejected under 35 U.S.C. § 102(b) as being anticipated by JP4112832 (Reference of record, "B4"; hereinafter "the '832 document).

The English language abstract of the '832 document discloses a composition containing "platinum" and "hydroxyapatite" (HA) as an *antiulcer* agent. The '832 document does not teach whether the "platinum" containing composition described in the '832 document is also an antitumor agent. Nor does it disclose the use of HA particles having a maximum size of 5 μm.

Claim 1 has been amended, rendering moot the rejection of Claims 1-3, 9 and 10. Independent Claim 1, as amended, recites: "An antitumor formulation, comprising an antitumor agent and hydroxyapatite particles having a maximum size of 5 μm, said antitumor formulation having reduced toxicity while maintaining the antitumor effects..." The '832 document does not disclose HA particles having the maximum size of 5 μm. Nor does it teach how to use such particles to reduce unwanted toxicity associated with an antitumor agent. Therefore, Claim 1, as amended, and other claims that depend from Claim 1 are not anticipated by the teachings of the '832 document.

Rejection of Claims 1-3, 9 and 10 Under 35 U.S.C. § 102(b)

Claims 1-3, 9 and 10 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Mohri *et al.* (*Japan J. of Cancer Chemotherapy* 1999 26:1791-1793; Reference of record "C3"; hereinafter, "Mohri").

Mohri teaches the use of HA particles loaded with cisplatin for intraperitoneal administration in rats. Mohri does not disclose whether the presence of HA particles reduces toxicity of cisplatin without affecting the antitumor effects. Nor does it teach the use of HA particles having a maximum size of 5 μm.

As noted above, Claim 1 has been amended, rendering moot the rejection of Claims 1-3, 9 and 10. Independent Claim 1, as amended, recites: "An antitumor formulation, comprising an antitumor agent and hydroxyapatite particles having a maximum size of 5 μm, said antitumor formulation having reduced toxicity while maintaining the antitumor effects..." Mohri does not teach the use of HA particles having a maximum size of 5 μm to reduce toxicity of cisplatin without affecting its antitumor effects. Therefore, Claim 1, as amended, and other claims that depend from Claim 1 are not anticipated by the teachings of Mohri.

Rejection of Claims 1-3 and 10 Under 35 U.S.C. § 102(b)

Claims 1-3 and 10 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Nakatani *et al.* (Japan J. of Cancer Chemotherapy 1992, 19:1644-1647; Reference of record "C4"; hereinafter, "Nakatani").

Nakatani discloses the slow release property and anti-tumor effects of adriamycin-mixed with HA *in vitro*. Nakatani does not disclose whether the presence of HA particles reduces toxicity of adriamycin. Nor does it teach or disclose the use of hydroxyapatite particles having a maximum size of 5 μm.

Independent Claim 1, as amended, now recites: "An antitumor formulation, comprising an antitumor agent and hydroxyapatite particles having a maximum size of 5 μm, said antitumor formulation having reduced toxicity while maintaining the antitumor effects..." Like the '832 document and Mohri, Nakatani does not disclose the use of HA particle having a maximum particle size of 5 μm. Nor does it teach that the presence of HA particles, particularly having a maximum size of 5 μm, could reduce toxicity of an antitumor agent. Simply, Nakatani fails to disclose the use of HA particles having a maximum size of 5 μm to reduce toxicity of an antitumor agent. Therefore, Claim 1, as amended, and other claims that depend from Claim 1 are not anticipated by the teachings of Nakatani.

Rejection of Claims 1-10 Under 35 U.S.C. § 102(b)

Claims 1-10 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Aoki *et al.* (Aoki *et al.*, *Transactions of the Materials Research Society of Japan.*, 15A: 3-9 (1994); Reference of record "C1"; hereinafter, "Aoki").

Aoki discloses a composition of carcinostatic substance loaded on HA particles and anti-tumor effects of the compound *in vitro*. Aoki, however, does not disclose whether the presence of HA particles reduces toxicity of adriamycin.

As noted above, Claim 1 has been amended, rendering moot the rejection of Claims 1-3 and 10. Independent Claim 1, as amended, recites: "An antitumor formulation having reduced levels of unwanted adverse effects without affecting desired antitumor effect, comprising an antitumor agent having predetermined levels of unwanted adverse and desired antitumor effects, said antitumor agent blended with hydroxyapatite particles having a maximum size of 5 μm..." Because Aoki does not disclose the use of HA particles to reduce unwanted toxicity of an antitumor agent, Claim 1, as amended, and other claims that depend from Claim 1 are not anticipated by the teachings of Aoki.

Rejection of Claims 1-10 Under 35 U.S.C. § 102(b)

Claims 1-10 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Lee *et al.* (WO 2002/41844; Reference of record "B1"; hereinafter, "Lee"). The Examiner stated that: "Lee et al. disclose compositions of nanocrystalline calcium phosphate paste with anti-cancer agents thus anticipating instant claims 1-4 (Abstract; pages 13-16 and claims 22-41)." (Office Action, Page 7).

Lee discloses drug delivery vehicles containing an anticancer agent and various types of calcium phosphates. Lee does not teach the use of HA particles to reduce toxicity of an antitumor agent. In Examples 5 an 6, Lee reveals the effects of cisplatin loaded onto a mixture of nonchrystalline calcium phosphate (NCP) and dicalcium phosphate dihydrate (DCPD) (50%:50% by weight) on growth of a breast tumor and a prostate tumor (*see* Lee, Figs. 1 and 3). However, neither NCP nor DCPD used by Lee is hydroxyapatite. Rather, these are calcium phosphates which possess an apatite structure ("apatite") and whose method of making is described in Lee at page 27, line 4 through page 28, line 6. Lee refers to them as "apatitic calcium phosphate drug delivery agent" (Lee at page 27, lines 4-6). In comparison, the present application demonstrates the use of HA to reduce toxicity of an antitumor agent and also use calcium triphosphate as a negative control that does not have any significant effect on reducing adverse effect (*see* the Specification at page 7, lines 33-36).

Presently, independent Claim 1 has been amended to recite: "An antitumor formulation, comprising an antitumor agent and hydroxyapatite particles having a maximum size of 5 μm, said antitumor formulation having reduced toxicity while maintaining the antitumor effects..." As noted above, Lee does not teach that the presence of HA particles effectively reduces toxicity of an antitumor agent while maintaining the desired antitumor effect.

Further, although Lee teaches the use of calcium phosphates, the use is directed to "cement" or "paste" that sets into a product upon mixing with an antitumor agent before injection. The reference does not disclose how to make a formulation suitable for, for example, oral administration. It is noted that Claims 2, 16 and 20 are directed to a formulation or a method of reducing toxicity of an antitumor agent for oral administration.

For the foregoing reasons at least, Lee does not anticipate Claim 1, as amended, and other claims that depends from Claim 1.

Rejection of Claims 1-10 Under 35 U.S.C. § 103(a)

Claims 1-10 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Lee. The Examiner states that: "the difference between the instant application and Lee et al. is that Lee et al. do not expressly teach all of the antitumor agents in instant claims 3 and 4. This deficiency in Lee *et al.* is cured by common sense" (Office Action, Page 9).

As noted above, Claim 1 has been amended, rendering moot the rejection of Claim 1 and other claims that depend from Claim 1.

Claim 1, as amended, is not rendered obvious over Lee because Lee does not teach or suggest that the presence of HA ($Ca_{10}(PO_4)_6(OH)_2$) particles having a maximum size of 5 μm reduces unwanted toxic effects of an antitumor agent that is, otherwise, known to exert toxic effects at a given dosage regimen. Specifically, Lee does not teach or suggest that toxicity of an antitumor agent can be reduced by providing HA particles having maximum size of 5 μm and blending and pulverizing them with an antitumor agent. In Lee (*e.g.*, Examples 4-6), the chemical composition and physiological property (*e.g.*, biodegradability) of calcium phosphate ($Ca_3(PO_4)_2$) and its derivatives, such as dicalcium phosphate dihydrate (DCPD), are different from those of hydroxyapatite. Further, Lee does not motivate one of skill in the art to use HA as a carrier for such purposes. Absent specific knowledge on the desirable properties of HA in reducing toxicity, one of ordinary skill in the art would not have been motivated to modify the teachings of Lee to arrive at the claimed invention. Lee is silent on these properties of HA in reducing toxicity.

Moreover, the claimed invention achieves unexpected results which would overcome any presumption of obviousness. For example, the present application teaches that: "For comparison, tests using other calcium phosphates were performed, and a slight reduction of toxicity in pulverized, tricalcium phosphate-supplemented sobuzoxane antitumor agents was observed. However, the reduction was not as great as that observed with pulverized hydroxyapatite-supplemented sobuzoxane antitumor agent" (the Specification at page 35, lines 2-5). Further, throughout the Specification, calcium triphosphate was employed as a negative control that does not exert any significant effect on reducing toxicity of antitumor agents (*see* the Specification at page 7, lines 33-36). These results effectively demonstrate that HA particles possess unexpected superior qualities in reducing toxicity of an antitumor agent as compared to

other calcium phosphates conventionally used as drug carriers. Throughout the Specification, these unexpected and surprising results are supported by empirical evidence. Thus, even assuming, *arguendo*, that a *prima facie* case of obviousness has been established, the claimed invention effectively overcome such obviousness.

At least for the foregoing reasons, Claim 1, as amended, and other claims that depend from Claim 1 are not rendered obvious in view of the teachings of Lee.

Double Patenting Rejection

Claims 1-10 have been provisionally rejected as being unpatentable on the ground of non-statutory obviousness-type double patenting over Claims 1-8 and 11 of copending Application No. 11/887,710 (hereinafter, "the '710 application").

In this application, Claim 7 has been canceled, rendering the rejection moot against Claim 7. Claims 1-6 and 8-10 have been amended as discussed above and the claims, as amended, no longer recite the same subject matter of the '710 application. However, to expedite prosecution, Applicants will consider filing a Terminal Disclaimer to obviate any "obviousness-type" double patenting rejection, as appropriate, upon notice of allowable subject matter in either application. This will permit Applicants to assess the rejection in view of the claims as ultimately indicated to be allowable, since it is possible that the claims may change during the course of prosecution.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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